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CHAPTER 79
Metformin

Alan J. Garber

Guanidine compounds, in the form of folk cures containing *Galega officinalis* (goat's rue or French lilac), were used to treat diabetes mellitus (DM) as early as medieval times (1). Because the administration of refined guanidine, the active agent in *Galega* preparations, produced unacceptable gastrointestinal toxicity, derivatives such as diguanides (the combination of two guanidine molecules with an intermediate chain) and biguanides (two linked guanidine molecules less an ammonia radical) were synthesized in the early part of this century. Although used in clinical practice for a number of years, they were rapidly displaced by insulin soon after its discovery.

With the introduction of sulfonylureas in the 1950s, there was renewed interest in the use of oral antihyperglycemic agents; clinical studies of biguanides, including phenformin, buformin, and metformin, were initiated. Phenformin, the first biguanide to achieve wide clinical acceptance, was used extensively in the United States and Europe during the 1960s and 1970s, but was withdrawn from most countries by 1978 because of an excessive risk of lactic acidosis and concerns about adverse cardiovascular effects that were documented in studies such as the University Group Diabetes Program (UGDP) trial (2,3). Unlike metformin, phenformin is cleared partially by the liver at variable rates, which allows for potential drug accumulation that may promote the development of lactic acidosis (4–6). Although metformin and phenformin have clinically significant differences in chemical structure and pharmacokinetic characteristics, fear of lactic acidosis and the reports of the UGDP effectively impeded the regulatory process for metformin in the United States. However, metformin was widely used in Europe, Latin America, and Canada, where more than 30 million patient-years of clinical experience showed it to be a safe and effective agent for the treatment of hyperglycemia in patients with type 2 DM. In the 1980s, a number of studies showed that metformin improved hyperglycemia in part through enhancements in insulin sensitivity. Moreover, it also became evident that metformin had beneficial effects on dyslipidemia and did not cause weight gain or hypoglycemia, features that prompted its reexamination in the United States. However, the relevance of these benefits to nonobese patients with type 2 DM was underappreciated and use of metformin in Europe was largely confined to obese patients.

The results of a number of studies, in association with the U.S. research effort on metformin, have clarified our under-

standing of its actions and of its role in the treatment of patients with type 2 DM. Metformin is now viewed as an agent that improves insulin resistance, one of the primary defects of type 2 DM, by improving the sensitivity of the liver and muscle to insulin. Additional studies in obese patients with type 2 DM, particularly the landmark United Kingdom Prospective Diabetes Study (UKPDS) (7,8), have also demonstrated favorable effects of metformin on consequential nonglucose parameters of cardiovascular risk (e.g., body weight, lipid profiles, and fibrinolysis), all of which were associated with significantly improved long-term clinical outcomes. This chapter briefly reviews the mechanisms of metformin action, outlines the pharmacodynamic effects of metformin on parameters of glucose metabolism and various cardiovascular risk factors in clinical trials, and describes current therapeutic approaches with metformin, including strategies for optimizing DM control using regimens of metformin monotherapy and combination therapies of this agent with other oral agents and with insulin.

EARLY CLINICAL OBSERVATIONS WITH METFORMIN

By the late 1960s, it was recognized that although sulfonylurea therapy for type 2 DM stimulated insulin secretion and was associated with hypoglycemia and excess weight gain, metformin did not promote insulin secretion or cause weight gain or hypoglycemia (9). Subsequently, because patients of normal weight appeared more tolerant of weight gain, clinicians used metformin in obese patients almost exclusively, although it was also used occasionally as a rescue agent in nonobese patients. Many studies of metformin from the 1960s and early 1970s included only obese patients (10) and may be unreliable because of small patient numbers, the use of patients with poorly characterized disease states, and inconsistent inclusion of appropriate experimental control subjects. In addition, aggressive glycemic control using modern intensive techniques was not available to patients of this era, who were able to monitor glucose concentrations only in urine—home (capillary) blood glucose testing was not yet available—and the measurement of hemoglobin A_{1c} (HbA_{1c}) concentrations was unknown.

A number of studies from this period confirmed that metformin was as effective as sulfonylureas in reducing fasting plasma glucose (FPG) concentrations (9–14). According to a meta-analysis of these early trials and several later studies, both metformin and sulfonylureas reduce FPG concentrations by 23 to 32 mg/dL and postprandial glucose concentrations by approximately 133 mg/dL (15). Although these early studies showed metformin monotherapy effective in both obese and nonobese patients (9,11), the prevailing attitude among European practitioners was that "the main indication for metformin is non-insulin-dependent diabetes associated with obesity and/or hyperlipidemia. Administration as a monotherapy is not unanimously recommended except in the very obese" (16).

After the near-total worldwide withdrawal of phenformin that followed publication of the UGDP data, metformin was reevaluated as a therapy for DM. Studies performed in the 1980s began to investigate the precise mechanisms of action of metformin (17), emphasizing the differences between metformin and the sulfonylureas. With the recognition of the important role of insulin resistance in the pathogenesis and natural history of type 2 DM, the apparent beneficial action of metformin on this defect afforded a greater impetus to research into this agent. The realization that metformin had beneficial effects on multiple aspects of the syndrome of insulin resistance, such as dyslipidemia, altered fibrinolysis, and obesity, renewed interest in metformin in the United States spurred therapeutic evaluations of metformin in large-scale, prospective, double-blinded, controlled clinical trials.

Effects of Metformin on Insulin Resistance and Gluconeogenesis

Patients with type 2 DM are characterized by resistance to the actions of insulin in both the liver and muscle, resulting in excessive basal and postprandial hepatic glucose production, and diminished insulin-mediated glucose uptake in peripheral tissues (18). A number of studies have demonstrated that the primary antihyperglycemic action of metformin results from improved insulin sensitivity, primarily in the liver and secondarily in muscle. Taken together, these improvements appear to increase glucose utilization by 20% to 53% (19–25). This increase in insulin-stimulated glucose utilization has been attributed to increased nonoxidative glucose disposal in the liver, such as through the formation of glycogen by glycogenesis and the increased incorporation of glucose into triglyceride (17,23,26). Furthermore, metformin-associated reductions of hyperglycemia were produced despite normal or, more likely, reduced plasma insulin concentrations (17,19–22,24–31). A number of studies examined the effect of metformin on hepatic glucose metabolism in animals and humans. They concluded that metformin inhibited hepatic glucose production, specifically gluconeogenesis from three carbon precursors, in a dose-dependent manner. However, this effect required the presence of insulin (32). Patients with type 2 DM characteristically exhibit accelerated gluconeogenesis as a key element of their hyperglycemia. This condition may result from elevated free fatty acid concentrations in patients with poorly controlled DM, increased rates of free fatty acid and lipid oxidation, or excessive glucagon secretion. It is therefore of potential importance that a number of studies have shown that metformin reduces plasma free fatty acid concentrations and slows the rate of lipid oxidation (19,21,23,29,33). Thus, metformin may act both directly and indirectly to inhibit hepatic gluconeogenesis.

In addition to its effects on the liver, metformin also appears to reduce glucose concentrations by reducing peripheral insulin resistance and augmenting insulin-mediated glucose uptake (17,34). The precise mechanism of this mode of metformin's action is incompletely understood but appears to involve multiple effects, including an increase in the number of insulin receptors or enhanced insulin–insulin receptor binding affinity in fat, muscle, and circulating blood cells (32). Metformin also enhances insulin receptor kinase activity (35) and stimulates glucose transport by increasing the activity or genetic expression of the GLUT-4 glucose transporter (19,36).

Effects of Metformin on Parameters of Lipid Metabolism

Results from early studies of metformin in patients with type 2 DM revealed beneficial effects on lipid metabolism. Interestingly, these observations were gathered from trials conducted in volunteers with and without DM (19,21,37–39). Reductions in triglyceride concentrations were consistently observed, with a decline of 10% to 20% commonly seen in patients with mild hypertriglyceridemia. In patients with substantially elevated triglyceride concentrations, however, greater reductions, possibly as much as 50%, may be noted. Reductions of total cholesterol concentrations in these early studies were more modest (37,40), whereas effects on high-density lipoprotein (HDL) cholesterol were variable (19,41).

CONTROLLED CLINICAL TRIALS EVALUATING METFORMIN

The large-scale U.S. trials evaluating the safety and efficacy of metformin as a treatment for type 2 DM provided a benchmark for evaluating metformin, both as a monotherapy agent and for use in combination with other agents for the treatment of type 2 DM. A number of randomized, double-blinded, placebo-controlled studies have evaluated the efficacy and tolerability of metformin monotherapy (42–45). These studies enrolled obese patients with type 2 DM who had inadequate glycemic control with dietary therapy alone and who received 1,700 to 3,000 mg metformin daily. Compared with those patients receiving placebo, mean FPG concentrations decreased by 52 to 92 mg/dL in patients receiving metformin and average HbA_{1c} concentrations were reduced by 1.4% to 1.9%.

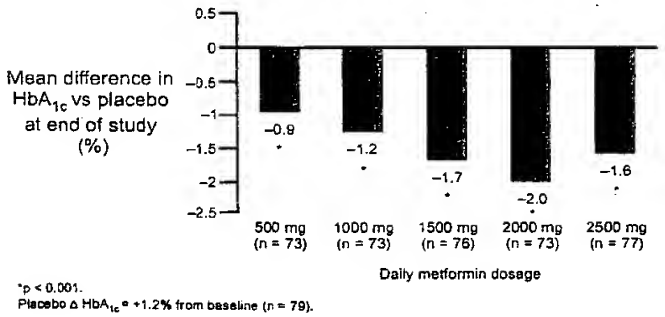
The dose–response characteristics of metformin therapy have been carefully examined in a robust, placebo-controlled, multicenter study (43). In this 14-week, double-blinded trial, 451 patients randomly received therapy with either placebo or 1 of 5 metformin dosages: 500 mg four times a day, 1,000 mg (500 mg twice daily), 1,500 mg (500 mg three times a day), 2,000 mg (1,000 mg twice daily), or 2,500 mg (1,000 mg with breakfast, 500 mg with lunch, and 1,000 mg with dinner). A log-linear, dose-dependent reduction in FPG and HbA_{1c} concentrations was observed in metformin-treated patients compared with those receiving placebo (Fig. 79-1). Compared with placebo, metformin reduced mean FPG concentrations by 19 mg/dL at the 500-mg daily dose and by 78 mg/dL at the 2,000 mg/day dose. HbA_{1c} concentrations were likewise reduced in a dose-dependent manner, falling 0.9% at the lowest dose and by 2.0% at the 2,000-mg daily dose. Based on this study, which is the first carefully controlled dose–response trial published with metformin, it would appear that for most patients, the 2,000-mg daily dose of metformin is most effective; however, a larger dose of 2,500 mg might prove beneficial for some patients with high baseline FPG and HbA_{1c} concentrations. This dose–response study also found that the incidence of adverse gastrointestinal effects was not dose related and did not increase with increasing metformin doses (43) (Table 79-1). Approximately 25% of patients experienced some adverse effects, but only 4% to 5% of patients discontinued therapy. Results of another study show that metformin-induced lipid reduction and weight loss are also dose related, increasing with dose up to (and beyond) the U.S. maximum of 2,550 mg/day (46). Thus, it is evident that metformin, unlike sulfonylureas, which have a relatively flat dose–response curve (47), shows a dose response that is clearly log-linear to 2,000 mg/day, with a minimum effective dose of 500 mg/day (43). Incremental titration is therefore almost always beneficial with metformin.

Metformin and Sulfonylureas: Comparison and Combination Therapy

A number of studies have compared metformin use with sulfonylureas (15,27,45,48–51). In each of these trials, the results indicated that metformin and sulfonylureas had equivalent antihyperglycemic activities. However, in these studies, metformin therapy was associated with either no change in weight or a reduction in mean body weight, whereas sulfonylurea treatment was associated with weight increases ranging from 2.8 to 5.3 kg (11,27,42,45). Increased insulin levels were associated with sulfonylurea therapy (27), whereas unchanged fasting and postprandial insulin concentrations were seen in the metformin cohorts in these studies (19,27,42).

Combination therapy using metformin and a sulfonylurea has been evaluated in a number of studies, usually by adding metformin to the regimens of patients with inadequate glycemic control despite therapy with maximally effective doses of sulfonylureas. In general, an additive reduction of FPG and HbA_{1c} concentrations is achieved by the metformin and sulfonylurea combination (27–29,52–55). In one of the largest of these studies (52), 1,823 patients with poor glycemic control despite sulfonylurea monotherapy received metformin in doses ranging from 850 to 2,550 mg/day. After 12 weeks, the mean HbA_{1c} concentrations of metformin-treated patients decreased by 1.9% and average FPG concentrations fell by 29% (both $p < .001$). In another study, however, Hermann and colleagues (54) reported findings of lesser efficacy. This study evaluated several different combinations of low- and high-dose metformin and glyburide therapy. In patients previously receiving glyburide, metformin was added to their treatment regimen. On the other hand, glyburide was added to patients previously receiving metformin. Metformin and glyburide monotherapy and combination therapies were also assessed in patients failing dietary therapy or oral antidiabetic therapy at baseline. Glycemic control improved in all treatment groups, but there were no significant differences between the various glyburide and metformin monotherapy and combination therapy regimens.

The effects of metformin therapy were compared with those of sulfonylurea treatment in the pivotal U.S. trials, as described by DeFronzo and colleagues (45). In these studies, metformin was compared with placebo in patients with type 2 DM [illegible]



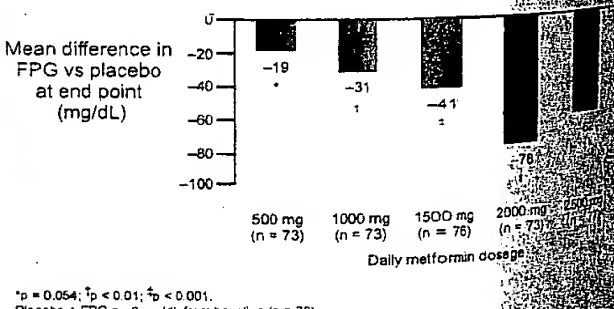


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Figure 79-1. Dose-related enhancements of (A) hemoglobin A_{1c} (HbA_{1c}) and (B) fasting plasma glucose (FPG) concentrations with metformin monotherapy. (From Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 1997;103:491, with permission.)

TABLE 79-1. Significant drug-related adverse events occurring in at least 2% of patients in a randomized, placebo-controlled, dose–response study of metformin

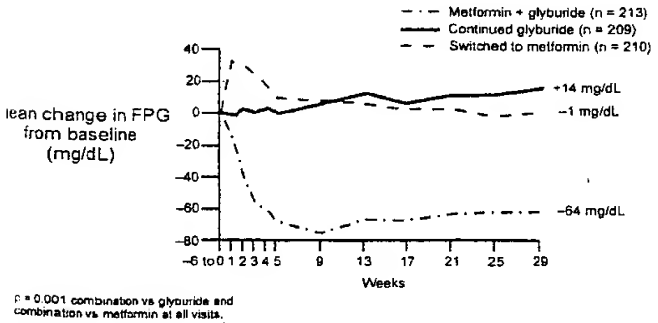
	Patients with adverse events					
		Metformin dose (mg/d)				
	Placebo (n = 79)	500 (n = 73)	1,000 (n = 73)	1,500 (n = 76)	2,000 (n = 73)	2,500 (n = 77)
Any adverse event[a]	15%	25%	30%	26%	27%	30%
Gastrointestinal disturbances[a]	13%	16%	29%	24%	23%	29%

[a] $p < .05$ for all doses of metformin versus placebo.

Data from Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 1997;103:491.

ad failed to maintain adequate glycemic control with dietary herapy. In the first protocol involving 289 subjects, 29 weeks of metformin monotherapy reduced baseline FPG and HbA_{1c} concentrations by 52 mg/dL and 1.5%, respectively, whereas both glycemic variables increased from baseline among placebo-treated patients (all $p < .001$). A separate protocol (n = 632) examined the effects of metformin monotherapy, glyburide monotherapy, and a metformin/glyburide combination in patients whose glucose values were not adequately controlled by glyburide therapy alone. In patients with secondary glyburide treatment failure, the substitution of metformin for glyburide did not produce any significant additional benefit in glycemic control. However, the addition of metformin to glyburide in combination therapy produced results superior to those with the use of either drug alone. FPG concentrations were reduced by an additional 63 mg/dL compared with metformin or glyburide monotherapy ($p < .001$; Fig. 79-2) and HbA_{1c} concentrations were reduced by an additional 1.7% ($p < .001$). The additive effect of metformin and glyburide on FPG values observed in this study is similar to the results of the previously described meta-analysis of European studies performed between 1957 and 1994 (15).

Complete reports of combination therapy trials of metformin and repaglinide, a short-acting sulfonylurea-like β-cell secretogogue, are not as yet published. However, in an analysis submitted for regulatory review (56), the addition of repaglinide to the regimens of patients poorly controlled with metformin produced an HbA_{1c} reduction of 1.4%.



gure 79-2. Reduction in fasting plasma glucose concentrations (FPG) ith metformin and glyburide monotherapy and combination therapy etformin and glyburide. (From DeFronzo RA, Goodman AM, Multicen- r Metformin Study Group. Efficacy of metformin in patients with non-sulin-dependent diabetes mellitus. *N Engl J Med* 1995;333:541, with ermission.)

Metformin and Other Oral Agents: Comparison and Combination Therapy

Metformin and Acarbose

Several studies have compared the use of metformin and acarbose, either alone or in combination (44,51,57,58). In one of these studies (44), metformin and acarbose as monotherapies were shown to be equally effective, although the glucose-lowering effect of metformin alone was much less than that seen in most other studies. When metformin was compared with acarbose as an add-on therapy in sulfonylurea-treated patients, both agents were also equally effective in lowering FPG and HbA_{1c} concentrations. On the other hand, results from another study of similar design (51) showed that metformin/sulfonylurea combination therapy was superior to acarbose/sulfonylurea therapy. In two additional studies, HbA_{1c} reductions of 0.65% to 0.8% were achieved when acarbose was added to the treatment regimens of patients with type 2 DM not adequately controlled by metformin alone (58,59). Evaluation of metformin/acarbose combination therapy, however, is complicated by acarbose-induced changes in metformin bioavailability: one study reported a substantial decrease in the bioavailability of metformin when combined with acarbose, presumably due to secondary effects of acarbose on the gastrointestinal motility or metformin absorption or both (60).

Metformin and Troglitazone

Only one small published clinical study has compared the effects of metformin and troglitazone (61). In this trial, patients with type 2 DM (n = 29) with secondary failure to sulfonylurea therapy were treated with metformin (2,000 mg/day) or troglitazone (400 mg/day), alone and in combination. When administered as monotherapies, metformin and troglitazone reduced FPG concentrations by approximately 20% and postprandial glucose concentrations by approximately 25%. When used in combination (troglitazone added to the therapy of patients treated with metformin, and vice versa), FPG concentrations were reduced by an additional 20%, approximately. Although both drugs are classified as insulin-sensitizing agents, these results suggest that their favorable effects on insulin resistance are mediated by different mechanisms In this study, assessments of the site of action of each agent were attempted. Troglitazone appeared to act primarily in muscle and adipose tissues, whereas metformin appeared to act primarily in the liver and secondarily in the muscle. Despite the reduction in fasting glucose levels with troglitazone monotherapy, no affect on hepatic insulin sensitivity was reported.

Metformin and Insulin

Because metformin enhances insulin sensitivity, is associated with weight loss, and does not cause hypoglycemia or an

increase in plasma insulin concentrations, the combination of an insulin sensitizer such as metformin with exogenous insulin may be an attractive therapeutic option for patients with type 2 DM who are poorly controlled using insulin alone. In numerous studies, this combination has been shown to enhance the effectiveness of insulin therapy—improving glycemic control or reducing exogenous insulin requirements—and to cause less weight gain than comparably effective regimens of insulin monotherapy, without an apparent increase in the frequency of hypoglycemic episodes (62–68). Thus, combination therapies using one or more oral agents may be of use with insulin because more than half of insulin-taking patients with type 2 DM are poorly controlled. In addition, the insulin dosage may be reduced. In one report, insulin therapy was discontinued in lieu of a metformin/sulfonylurea combination in 76% of patients with type 2 DM without any deterioration of glycemic control (62); however, the clinical utility of a reduction in insulin dosage is unclear.

In a 1998 study, Aviles-Santa and colleagues (65) evaluated whether addition of metformin to the regimens of insulin-treated patients with type 2 DM who had poor glycemic control would incrementally improve glycemic control compared with insulin monotherapy. Patients randomly received either metformin (titrated to a maximum dose of 2,500 mg/day based on tolerance and blood glucose concentrations) or placebo, and insulin doses were adjusted up or down as necessary to maximize glycemic control. Dietary advice was also offered on an ongoing basis. After 6 months, HbA_{1c} concentrations declined from 9.4% to 7.7% among patients treated with insulin and from 9.2% to 6.7% in the group receiving metformin with insulin ($p < .01$ when comparing treatment groups; Table 79-2). An increased frequency or dosage of insulin therapy did not account for the improvement in glycemic control in metformin/insulin-treated patients: over the study period, patients treated with metformin and insulin reduced their insulin dose by 2 U/day. By comparison, patients receiving insulin monotherapy required 32% more insulin at the end of the study to achieve yet a smaller reduction in HbA_{1c} values than those achieved in the metformin plus insulin group.

In a prospective, randomized, double-blinded trial, Bergenstal and colleagues (64) also observed a decrease in insulin doses and the number of injections required per day when metformin (1,000 mg twice daily) was added to patients with type 2 DM previously optimized insulin regimens (three injections per day). Despite achieving similar degrees of glycemic control after 4 months of therapy (HbA_{1c} concentrations of approximately 7.0%), metformin-treated patients required 36% less insulin ($p < .01$) and also required fewer daily insulin injections than patients treated with insulin and placebo. Approximately 20% of patients treated with insulin alone required four injections per day to maintain glucose concentrations within the target range, compared with only 4% of patients receiving insulin plus metformin. In addition, 8% of metformin/insulin–treated patients and none of the insulin/placebo patients were able to reduce their number of daily insulin injections from three to two. Finally, patients receiving both insulin and metformin lost weight (~3.2 kg) and had significantly lower total and low-density lipoprotein (LDL) cholesterol concentrations ($p < .01$) than patients treated with insulin alone. Weight gain in the insulin/placebo group averaged approximately 2.7 kg.

TABLE 79-2. Effect of metformin or placebo on hemoglobin A_{1c} concentrations and daily insulin dose in insulin-treated patients with type 2 diabetes mellitus

Variable	Placebo	Metformin
Hemoglobin A_{1c} (%)		
Baseline	9.4	9.2
6 Months	7.7[a]	6.7[a,b]
Daily insulin dose (U/day)		
Baseline	101.7	94.5
6 Months	129.2[c]	95.5

[a] $p < .01$ versus baseline.
[b] $p = .0116$ versus placebo.
[c] $p = .0120$ versus metformin.

Data from Bergenstal R, Johnson M, Whipple D, et al. Advantages of adding metformin to multiple dose insulin therapy in type 2 diabetes. *Diabetes* 1998;47(Suppl 1):A89(abst).

SAFETY AND EFFICACY OF METFORMIN IN LONG-TERM CONTROLLED CLINICAL TRIALS

The UKPDS, a landmark trial examining the benefits of intensive glycemic control policies and the use of differing agents (69) on hard end point parameters of the microvascular and cardiovascular complications of type 2 DM. In addition, therapies with insulin, metformin, or sulfonylurea were evaluated for particular advantages or disadvantages in people with type 2 DM. A total of 5,102 people newly diagnosed with type 2 DM (mean age, 53 years, with baseline HbA_{1c} concentrations of 9.1%) were enrolled and followed for an average of 11 years. Patients received either conventional therapy (with a treatment goal of achieving FPG concentrations < 270 mg/dL) or intensive therapy (treatment goal of FPG < 108 mg/dL). Patients in the conventional treatment group initially received dietary therapy alone, although most (80%) later required pharmacologic therapy to reach their glycemic target (8). Intensively treated patients were randomized to receive insulin, sulfonylureas, or metformin (if obese) as monotherapy. A total of 21 clinical end points were defined, including an aggregate "diabetes-related end point" encompassing sudden death, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation of at least one digit, vitreous hemorrhage, retinal photocoagulation, cataract extraction, death from hyperglycemia or hypoglycemia, and a combined end point of serious microvascular complications.

By the end of the study, with an average patient follow-up time of 11 years after randomization, the intensively treated patients had achieved a median HbA_{1c} concentration of 7.0% compared with 7.9% in conventionally treated patients (8). This improvement in glycemic control was associated with a 12% risk reduction for any DM-related end point, and a 25% reduction in the risk of microvascular complications. Overall, intensive therapy was not associated with a statistically significant reduction in cardiovascular end points, although a strong relationship between macrovascular complications and degree of glycemia emerged on epidemiologic analysis.

All therapies in the intensively treated group were equally effective, with no difference in HbA_{1c} concentrations between groups (8). Of the agents used in a separate randomization in obese patients that included metformin, metformin was the only agent associated with a significant improvement in clinical endpoints. Patients receiving metformin (Fig. 79-3) had a 21% reduced risk of any DM-related end point, a 36% reduction in all-cause mortality, and 41% reduction in stroke ($p = .003$, .017, and .032, respectively, vs. other intensive therapies). In a substudy initiated after the trial had already begun, the addition of metformin was evaluated in a controlled manner in secondary sulfonylurea failure patients. Metformin addition was associated with an increased risk of DM-related death compared with treatment with sulfonylureas alone. This finding appeared

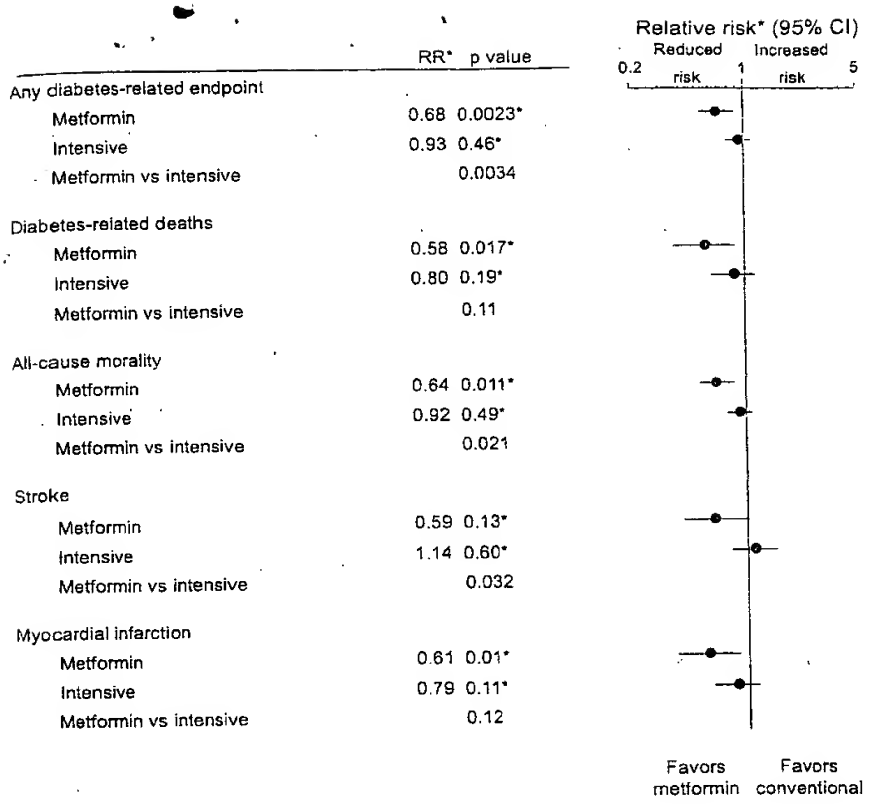


Figure 79-3. Comparison of clinical outcomes with metformin and other intensive therapy regimens in the United Kingdom Prospective Diabetes Study. RR, relative risk; CI, confidence interval. *, compared with conventional therapy. (From UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854, with permission.)

result from a lower-than-expected death rate in the sulfonylurea-only group rather than an increase in the event rate or mortality in the metformin/sulfonylurea combination group (70). The investigators concluded that this anomaly was likely a chance occurrence owing to low patient numbers and the small number of reported macrovascular events. To evaluate this result further, a combined analysis of all metformin-treated patients in the UKPDS showed that metformin therapy was associated with 19% fewer DM-related end points (p = .033).

Taken as a whole, the UKPDS investigators concluded that the trial data supported the view that metformin may be the first-line pharmacologic therapy for diet-failed, overweight patients with type 2 DM (7). The basis for the apparent improvements in the metformin monotherapy cohort with regard to macrovascular events cannot result from differential efficacy in glycemic control because all agents in the intensive policy groups were equally effective in achieving glycemic control. The observed event reductions are more likely the result of the favorable effects of metformin on known parameters of cardiovascular risk such as body weight, lipid profile, fibrinolysis, and hyperinsulinemia, and hypoglycemia.

Tolerability and Safety

Gastrointestinal disturbances are the most common adverse events associated with metformin, occurring in 5% to 20% of patients (see Table 79-1), and diarrhea is the most common symptom. Nausea, vomiting, abdominal bloating, metallic taste, flatulence, and anorexia have also been reported. Overall, 25% of patients experience an adverse event within the first months of therapy, but only 4% to 5% have to discontinue the agent (43). These symptoms, usually gastrointestinal in nature, are transient and usually resolve spontaneously after a few weeks of treatment. The severity or occurrence of these gastrointestinal effects is not related to dose (43). Multiple clinical studies show that fewer than 5% of patients are unable to tolerate metformin as a result of gastrointestinal side effects (17,43,45,52,71).

Long-term metformin therapy may impair gastrointestinal absorption of vitamin B_{12} and folic acid (45,72,73). If absorption of vitamin B_{12} is impaired, this may lead to increased serum concentrations of total homocysteine, a risk factor for atherosclerosis. In a prospective study enrolling 50 nondiabetic male patients with cardiovascular disease, metformin treatment caused a reduction in vitamin B_{12} and folic acid concentrations, and an increase in homocysteine concentrations (73). However, another study involving patients with type 2 DM determined that the effect of metformin on homocysteine concentrations, if any, was likely to be small (74).

Concern regarding the potential of metformin to cause lactic acidosis, the serious condition that prompted the removal of phenformin worldwide, has lessened because of the low incidence of this problem in the United States since metformin's introduction. Unlike phenformin, metformin does not alter the rate of plasma lactate turnover but actually increases lactate oxidation (75). Metformin does not undergo significant hepatic metabolism, but is cleared by the kidney. In comparison, phenformin is cleared partially by the liver and a significant percentage of people (~9%) have genetic polymorphisms resulting in slow phenformin hydroxylation, which allows for drug accumulation that may promote the development of lactic acidosis (4–6). In addition, metformin is less lipophilic than phenformin and does not readily penetrate lipid membranes or accumulate in mitochondria, factors thought to contribute to the development of lactic acidosis (17).

The risk of lactic acidosis in metformin-treated patients is very low, occurring at a rate of 3 cases per 100,000 patient-years

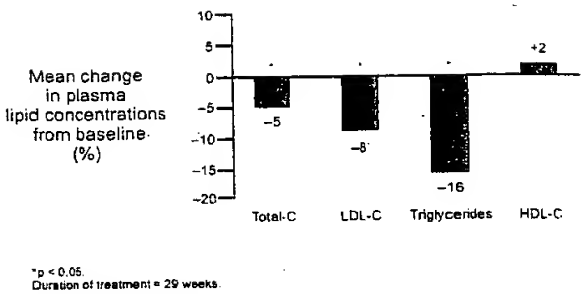
(32,76–79). An analysis of lactic acidosis rates in U.S. patients with type 2 DM before the approval of metformin found a background rate of lactic acidosis of 9.7 episodes per 100,000 patient-years. This is actually a higher incidence than that currently seen in association with metformin therapy (78). However, the difference may likely be inconsequential. In this study, as in others evaluating the incidence of lactic acidosis associated with metformin (76,79–82), virtually all of the patients with confirmed or probable lactic acidosis events had severe intercurrent illnesses that can themselves cause lactic acidosis. The incidence of lactic acidosis in metformin-treated patients is lower than the incidence of hypoglycemic coma in patients treated with glyburide, although both conditions have comparable mortality rates (80).

Most of the cases of metformin-associated lactic acidosis have been reported in patients in whom metformin was contraindicated, such as a severe, concomitant medical disorder—sepsis, heart failure, liver disease, pulmonary failure, tissue hypoxia, or hypotension—or the presence of acute or chronic renal failure (76,83–85). Among those with confirmed acidosis, an absence of overt risk factors has been documented in only a very small number of cases (76,86–88). This accumulation of clinical and epidemiologic data suggests that metformin use may not necessarily be an independent risk factor for lactic acidosis (78,84). It is possible, too, that because physicians are more alert to the possibility of lactic acidosis in patients receiving metformin, they are more diligent in obtaining a diagnostic serum lactate measurement in these patients, thereby uncovering episodes of lactic acidosis that may have gone undiagnosed in patients receiving another drug.

Metformin should be used with caution in the elderly, and only with creatine clearance measurements to determine that renal function is adequate for drug excretion. Metformin should not be given to patients with evidence of hypoxemia, dehydration, or sepsis. The withdrawal of metformin during procedures involving iodinated contrast materials is somewhat controversial. Current practice with metformin is to discontinue its use before or at the time of the contrast procedure and to withhold metformin for an additional 48 hours to assess adequacy of renal function after the procedure. However, several reports suggest that such withdrawal may not be necessary in patients with normal renal function because they have a very low incidence of contrast media–induced renal insufficiency (89,90).

To reduce the risk of gastrointestinal side effects, metformin therapy should be initiated at a low dose and gradually titrated upward until the maximal dose (2,550 mg/day) is reached or target glycemic goals are achieved. Administering metformin with meals also reduces the incidence and severity of gastrointestinal symptoms. Therapy may be initiated with either one 500- or 850-mg tablet taken at breakfast, or with one 500-mg tablet administered at breakfast and dinner (lunch and dinner if no breakfast is eaten). The dose should be increased gradually at intervals of no closer than 1 week, because the full antihyperglycemic effect may require as much as 1 week to manifest. The maximum recommended U.S. dosage is 2,500 mg (five 500-mg tablets/day) or 2,550 mg (three 850-mg tablets/day). Higher dosages are sometimes used outside the United States.

Metformin has well documented effects on lipid and lipoprotein levels in both diabetic and nondiabetic people (Fig. 79-4). Metformin exerts its greatest effects on triglyceride concentrations, with reductions in the range of 15% to 25% typically noted, although reductions of up to 45% have been reported (19,21,40,42,45,46,67,68,91–97). These effects are greater in patients with more pronounced hypertriglyceridemia (42,45,67,97). It has been suggested that the effect of metformin on triglyceride levels is the result of decreased synthesis of very low density lipoprotein (VLDL) particles, whose concentrations



*$p < 0.05$.
Duration of treatment = 29 weeks.

Figure 79-4. Effects of 29 weeks of metformin monotherapy on plasma lipid concentrations. C, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein. (From DeFronzo RA, Goodman AM, Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995;333:541, with permission.)

are reduced after metformin therapy (17,19,21,96). A direct inhibitory effect of metformin on hepatic VLDL secretion has also been reported (19,21,98). Metformin therapy is also associated with modifications of lipoprotein composition such as a reduced amount of cholesterol in VLDL particles (98). Effects of metformin on LDL and total cholesterol concentrations have also been observed (19,21,40,42,45,46,67,68,91–97). Total and LDL cholesterol concentrations may be reduced by 5% to 10%, although larger reductions have been reported. In the United States, multicenter registration trial, metformin monotherapy reduced baseline LDL cholesterol and total triglyceride concentrations by 8% (45). HDL cholesterol concentrations are usually unchanged or slightly increased with metformin therapy (19,21,42,45,67,96–98). The lipid-lowering effect of metformin appears to be independent of its effect on glucose because metformin has been shown to reduce cholesterol and triglyceride concentrations in nondiabetic people as well (67,94–96,99).

The effect of metformin in combination with sulfonylurea therapy on lipid metabolism has also been examined. In a study examining postprandial lipemia, glipizide monotherapy (40 mg/day) reduced fasting and postprandial concentrations of triglyceride-rich lipoproteins in 18 patients with type 2 DM (100). Addition of metformin (mean dose, 2,300 mg/day) to this regimen ($n = 16$) further reduced plasma triglyceride concentrations from 2.63 to 2.07 mmol/L, a significant decrease when compared with glipizide monotherapy ($p = .02$) (21). Compared with sulfonylurea monotherapy, total cholesterol concentrations also fell significantly (from 4.90 to 4.64 mmol/L, $p = .002$), with a substantial reduction in VLDL cholesterol concentrations (1.15 vs. 0.80 mmol/L, $p = .005$). In another study, metformin (2,500 mg/day) and glyburide (20 mg/day) were given alone and in combination to 632 patients with type 2 DM (45). Glyburide alone had little effect on total, LDL, and HDL cholesterol concentrations, but substantially increased triglyceride concentrations. Metformin monotherapy reduced baseline concentrations of total cholesterol (5%), LDL cholesterol (8%), and triglycerides (8%), and increased HDL cholesterol concentrations slightly (2%). Combination therapy with metformin and glyburide also produced significant decreases from baseline in total and LDL cholesterol and triglyceride concentrations, but the magnitude of these changes were not greater than those seen with metformin alone, even though glycemic control was significantly improved. It has also been reported that withdrawal of metformin from combination therapy with sulfonylureas caused an increase in total and LDL cholesterol concentrations. When metformin was reintroduced, lipid and lipoprotein levels declined (40).

The lipid-lowering effects of metformin also appear to be dose related. In a placebo-controlled study comparing the effects of metformin 1,500 mg/day with metformin 3,000 mg/day, only the higher dose produced a statistically significant reduction in plasma triglyceride and cholesterol concentrations relative to placebo (46). Maximum reductions in fasting plasma insulin concentrations were achieved at a dose of 3,000 mg/day (46). However, the beneficial effects of metformin on fibrinolysis were the same at all doses (46). The lipid-lowering effect of metformin at doses up to 3,000 mg/day suggests that prescribing maximal doses of metformin may be justified for their beneficial effect on cardiovascular risk factors, even when a plateau for antihyperglycemic activity is reached.

Body Weight

Unlike sulfonylureas and insulin, both of which cause weight gain when given to patients with DM, metformin is weight-neutral or produces a weight loss of 0.7 to 3.8 kg in both diabetic (9,11,45,48,50,75,101–103) and nondiabetic people (93,102,104, 105). Most of the weight loss (typically a 1% to 3% reduction from pretreatment weight) occurs in the first 3 to 6 months of therapy (17). This weight loss may also be additive with any weight loss resulting from diet, but it is not metformin dose related. A number of mechanisms have been postulated by which metformin might contribute to weight loss, including decreasing food consumption (103), increasing thermogenic activity of brown adipose tissue, increasing futile cycling of substrates (17), enhancing carbohydrate utilization in the gastrointestinal tract, adverse gastrointestinal side effects, carbohydrate malabsorption (91), and reducing hyperinsulinemia (102). Which of these possibilities, if any, is correct is unclear. Metformin may not affect concentrations of leptin (105).

Fibrinolysis

Patients with insulin resistance, type 2 DM, or both exhibit impaired fibrinolysis and have elevated plasminogen activator inhibitor-1 (PAI-1) concentrations, both of which indicate the presence of a hypercoagulable state and are risk factors for cardiovascular disease. Metformin therapy has been shown to reduce PAI-1 concentrations by approximately 20% (42,46, 86,93,99). This effect may be secondary to decreased thromboglobulin concentrations and thromboxane B_2 activity, decreased plasma fibrinogen concentrations, or increased fibrinolytic activity (106).

Use of Metformin in Insulin-Resistant, Prediabetic Patients

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of chronic anovulation and infertility in American women; it affects 6% of reproductive-age women in the United States. Women with PCOS typically exhibit hirsutism and oligomenorrhea or amenorrhea, and are anovulatory. Approximately half of these women are obese, but all have significant underlying insulin resistance as a primary cause of this illness independent of the presence of obesity. Other clinical abnormalities include increased concentrations of total and free testosterone, decreased serum sex hormone–binding globulin concentrations, increased serum luteinizing hormone (LH) concentrations, and hyperinsulinemia. Women with PCOS often exhibit other features of the insulin resistance syndrome, including central obesity, hypertriglyceridemia, reduced HDL cholesterol and PAI-1 concentrations, and hypertension.

The fundamental defect seen in women with this condition is increased ovarian production of testosterone. The increased androgen production has both local effects, causing premature follicular atresia and anovulation, and systemic effects, increasing serum testosterone concentrations. Normally, progesterone secreted by the ovaries is converted first to testosterone and then to estradiol, the latter reactions catalyzed by enzymes derived from cytochrome P450c17α. In women with PCOS, P450c17α activity is increased, resulting in elevated testosterone concentrations. It has been hypothesized that insulin resistance stimulates P450c17α activity, thereby increasing testosterone concentrations and the secondary changes found in women with PCOS. In studies of metformin administration to lean or obese insulin-resistant women with PCOS, P450c17α activity and serum free testosterone and LH concentrations were reduced. Metformin has also been shown to normalize free testosterone and 17α-hydroxyprogesterone concentrations, restore menstrual cycling, and normalize the altered plasma ratio of LH to follicle-stimulating hormone (107–112). In addition, metformin improves glucose tolerance and insulin sensitivity, reduces insulin concentrations, and promotes weight loss (107,109,110,113,114). However, metformin does not improve insulin sensitivity in all women with PCOS (115–117). Metformin may also restore ovulation and fertility. In several trials (109,110,112), metformin also increased the rate of spontaneous pregnancy in some women and, when used in conjunction with clomiphene, allowed 90% of women to resume normal menses (118).

Insulin Resistance Syndrome

The clinical features of the insulin resistance syndrome, or syndrome X, are impaired glucose tolerance, hyperinsulinemia, android pattern of body fat distribution, dyslipidemia, obesity, and hypertension. People exhibiting the insulin resistance syndrome are also at increased risk for cardiovascular disease, and the condition often progresses to overt type 2 DM (119–121). Because metformin improves insulin sensitivity, it has been used in clinical trials to prevent or delay the development of DM, and to reduce the risk of cardiovascular disease. In studies in patients with impaired glucose tolerance, metformin administration improved insulin sensitivity as measured by both the euglycemic hyperinsulinemic clamp technique and C-peptide concentrations (95,122–124). Metformin administration also improved dyslipidemia, fibrinolytic activity, and insulin sensitivity in patients with abdominal obesity (93,124,125). The Biguanides and Prevention of Risks in Obesity (BIGPRO-1) study compared the effects of metformin (850 mg twice daily) and placebo on obese nondiabetic subjects with android body fat distribution (93). After 3 years of therapy, metformin-treated patients had a lower body weight, fasting plasma insulin, LDL cholesterol, and tissue plasminogen activator concentrations compared with placebo-treated patients. In patients with impaired glucose tolerance at entry, metformin significantly lowered FPG concentrations as well. In addition, none of the metformin-treated patients acquired type 2 DM, whereas five placebo-treated patients did. These highly preliminary findings suggested the hypothesis that metformin may be useful in preventing the progression of impaired glucose tolerance to overt type 2 DM. In part for these reasons, the Diabetes Prevention Program (DPP), a large multicenter U.S. study that is now underway, is investigating whether intensive lifestyle intervention or metformin treatment can prevent the progression of impaired glucose tolerance to DM (126).

CONCLUSION

The role of metformin in the therapy of patients with type 2 DM has evolved as our understanding of the pathogenesis of

type 2 DM and its complications has evolved. Initially used as second-line therapy for sulfonylurea-failed obese patients, metformin is now often used as a first-line therapy, particularly in obese or dyslipidemic patients. Because cardiovascular complications are the leading cause of morbidity and mortality in patients with type 2 DM, it is now realized that effective treatment for the cardiovascular risk factors present in these patients is as important as glycemic control *per se* in reducing DM-related morbidity and mortality. Thus, because of the benefits on body weight, dyslipidemia, and other cardiovascular risk factors seen in multiple clinical trials, metformin has become a useful treatment option for patients with type 2 DM. Because of its treatment benefit for insulin-resistant states, metformin may be an important therapy for prediabetic states as well as for related conditions such as PCOS.

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CHAPTER 80
*Thiazolidinediones**

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To date, the treatment of type 2 diabetes mellitus (DM) has involved the use of insulin and/or insulin secretagogues such as sulfonylureas and/or biguanides such as metformin. Although these agents have been efficacious to a degree, they do not deal directly with the underlying pathology of insulin resistance.

The thiazolidinediones represent a novel drug class that may directly decrease insulin resistance by enhancing insulin action in skeletal muscle, liver, and adipose tissue. Three of these compounds—troglitazone, rosiglitazone, and pioglitazone—have been approved for use in the United States.

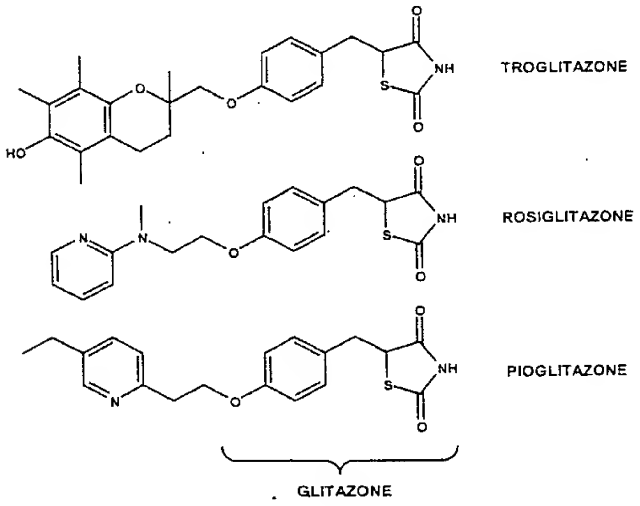

Figure 80-1. Structures of several thiazolidinedione insulin-sensitizing agents.

The structures of several thiazolidinedione compounds are shown in Fig. 80-1. All of these compounds contain a substituted thiazolidinedione structure, with modifications selected to improve their pharmacologic effects. Some of these modifications have significantly enhanced the bioactivity of these compounds, although it is not known whether their increased potency results from changes in bioavailability, metabolism, or mechanistic efficacy. Troglitazone was designed to combine the insulin-sensitizing activity of the thiazolidinedione class with a potent lipid peroxide-lowering activity. Lipid peroxides have been suggested as one of the major causative factors of atherosclerosis, and their concentrations are frequently elevated in diabetics, suggesting that troglitazone might be an especially effective agent for type 2 DM.

THIAZOLIDINEDIONES IMPROVE INSULIN SENSITIVITY IN ANIMAL MODELS OF DIABETES

Thiazolidinediones appear to enhance insulin action without directly stimulating insulin secretion in pancreatic β-cells. As such, these drugs have been used to assess the impact of lowering insulin resistance on a wide variety of pathophysiologic processes. These agents markedly decrease plasma glucose, insulin, and triglyceride concentrations in genetically insulin-resistant animals, including the KKa, *ob/ob*, and *db/db* mice, the Zucker *fa/fa* rat, and others (1–3). The antihyperglycemic activity of some thiazolidinediones has also been demonstrated in nongenetic insulin-resistance models, including both the fructose-fed and high fat diet-adapted rat (4,5). In contrast, plasma glucose concentrations are unaffected by these drugs in the insulin-deficient streptozotocin diabetic rat unless administered with concomitant doses of insulin. The thiazolidinediones, however, improve insulin sensitivity in these animals, as determined by increased glucose infusion and decreased hepatic glucose output in euglycemic clamp studies (6). Plasma glucose is similarly unaffected in normal animals, although thiazolidinediones still enhance insulin action in these animals, resulting in lower plasma insulin and lipid concentrations (7). These observations highlight the distinguishing feature of these insulin-sensitizing agents—the apparent lack of hypoglycemic activity in euglycemic animals despite the potent sensitization of insulin action. This property differentiates thiazolidinediones from other current therapies for type 2 DM, including insulin itself and insulin secretagogues such as sulfonylureas, which have considerable hypoglycemic activity.

To assess the mechanism of insulin sensitization in diabetic animal models, both glucose disposal and hepatic glucose output have been studied by the euglycemic hyperinsulinemic clamp technique after administration of the drugs. (4,8,9). In general, improvements in insulin sensitivity induced by thiazolidinediones require several days of treatment, suggesting that transcriptional modifications are involved in the actions of these drugs (see below). A number of metabolic processes have been evaluated in tissues from animals exposed to these agents. Chronic treatment of obese Zucker rats with troglitazone (unpublished) or pioglitazone (10) led to increased sensitivity and responsiveness of insulin-induced glucose uptake in isolated adipocytes from these animals. Similarly in Wistar fatty rats, pioglitazone produced an increase in insulin-stimulated glycogen synthesis and glycolysis assayed in isolated soleus muscle (11). Similar improvements in glucose uptake were observed with englitazone in obese Zucker rats (8). Additionally, the thiazolidinediones dramatically reduce hepatic glucose output in a number of diabetic models. These effects appear to result from a decreased rate of gluconeogenesis in the liver.

While thiazolidinediones in general do not directly stimulate insulin secretion in islet cells, the amelioration of

*Please see footnote on p. 804 regarding troglitazone.